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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/530,935	HEARING ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-17 and 19-37* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-17 and 19-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-7, 9-17, 19, and 21-37 are pending examination.

The applicants' traversal, the amendment to claims 1-7, 9-17 and 19 and the addition of claims 21-37 filed on 6/25/02 paper no. 12 is acknowledged and considered.

The substitute sequence listing filed on 7/15/02 paper no. 13 has been entered.

Election/Restrictions

Note: claim 20 is drawn to a non-elected invention (see paper no. 7) and applicants have not canceled this claim.

Specification

The objection to the disclosure is moot in view of the amendment to the specification in paper no. 12.

Claim Objections

The objection to the claims is moot in view of the amendment to the claims in paper no. 12.

The rejection under 101 for claims 8, 18, and claims dependent therefrom is moot in view of the amendment to the claims.

However, in view of the additions of claim 21 and claims dependent therefrom a new rejection under 101 follows:

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 21 and claims dependent therefrom are rejected under 35 U.S.C. 101 because the claims are not supported by either a well-asserted utility or a well-established utility.

Definitions: [from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS: repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Credible Utility" – Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, office personnel must determine if the assertion of utility is credible (i.e. whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based in inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific utility" – a utility that is *specific* to the subject matter claimed. This contrast with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what conditions can be diagnosed.

"Substantial utility" – a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying our further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic Research such as studying the properties of the claimed produce itself or the mechanisms in which the material is in involved.

B. A method of treating an unspecified disease or condition. (Note: this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor

substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. 101. This analysis should of course, be tempered by consideration of the context and nature of the invention. For example, if a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" – a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone, or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a non-specific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this were the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight, any carbon containing molecule would have a "well established utility" as a fuel since it can by burned; and any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

[See also the MPEP at 2107 –2107.02].

The claimed methods in claim 21 and claims dependent therefrom are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. The reason for this is that the only utility for the DNA delivery vector is for use in gene transfer to cells (See page 20 of the as-filed specification). The claimed method is not supported by a substantial utility because the disclosed use of the adenovirus vector is for delivering a nucleic acid to a cell and not packaging a helper adenovirus vector. The specification states, "It is a further object of this invention to provide a novel means to specifically repress the production of helper virus while allowing the production of an adenovirus vector during the preparation of the virus (page 4)." More specifically, the specification states, "The vectors of the present invention are useful in DNA delivery systems to help curb the production of replication competent adenovirus (RCA), a virus that is dangerous and potentially toxic to a patient receiving it during patient administration" (page 16)." Furthermore, the specification states, "The vector design also increases the safety of recombinant adenovirus vectors for use in DNA transfer by reducing the potential of replicant competent adenovirus (page 13)." The claimed

method in claim 21 and claims dependent therefrom do not have an identified substantial utility. In addition, in view of the claims, one skilled in the art would determine that packaging a helper adenovirus without a heterologous gene would require further research to identify and reasonably confirm a "real world" context of use and therefore, a substantial utility is not defined. Note: since the claimed invention is not supported by a substantial utility because of the reasons set forth above, credibility utility has not been assessed. In conclusion, neither the specification as filed nor any art of record discloses or suggests any property or activity for the packaged helper adenovirus vector in the claimed invention, such that is could be used in a method of expressing a heterologous gene in a mammal.

Applicants' traversal is not found persuasive to the rejection under 101 for the new claims because it is not applicable to the rejection set forth above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 and claims dependent therefrom are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim 21 and claims dependent therefrom are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New claim 21 filed on 6/25/02 introduces new subject matter into the disclosure. The application and the originally filed claims as a whole are directed to: A method of regulating adenovirus packaging comprising the following steps of: a. obtaining an adenovirus vector containing an adenovirus packaging repressor binding site, said binding site; and b. propagating said vector in the absence of said packaging repressor; and c. repressing packaging of said vector in the presence of said packaging.

New claim 21 for example, recites: A method of regulating adenovirus packaging comprising the steps of: a) obtaining a helper adenovirus vector containing a first adenovirus packaging sequence; b) obtaining a DNA delivery adenovirus vector comprising 5' and 3' ITRs, a second adenovirus packaging sequence comprising a repressor binding site; and a promoter operatively linked to a heterologous gene; c) propagating the helper adenovirus vector and the DNA adenovirus vector in a cell-line; and d) repressing packaging of the DNA delivery adenovirus vector by a repressor which binds to the repressor binding site contained in the DNA delivery adenovirus vector.

The full scope of the new claims is directed to a method of packaging a helper virus while repressing the packaging of a DNA delivery adenovirus vector. However, the as-filed specification as a whole neither teaches nor suggests nor contemplates this claimed method or products for use in said method. In fact, there is no paragraph cited by applicant for support of the newly added claims.

In addition, the specification states:

"It is a further object of this invention to provide a novel means to specifically repress the production of helper virus while allowing the production of an adenovirus vector during the preparation of the virus." Please see page 4 of the as-filed specification.

It is apparent form the as-filed specification and the cited paragraph on page 4, that applicant at the time the invention was made did not intend or contemplate a method of packaging a helper virus while repressing the packaging of a DNA delivery adenovirus vector. Thus, one skilled in the art on the basis of applicant's specification at the time the invention was made would not envision a method of packaging a helper virus while repressing the packaging of a DNA delivery adenovirus vector. Thus, there is no evidence that the applicant was in possession of the full scope of the invention of the new claims and claims dependent thereof, as it is now claimed, at the time the application was filed.

Applicants' traversal is not found persuasive because it is not applicable to the rejection under 112 new matter set forth above.

Claims 1-7, 9-17, 19, and new claims 21-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method of regulating adenovirus packaging of a replicant defective adenovirus vector comprising the steps of: A) obtaining an adenovirus vector containing an adenovirus packaging element comprising a repressor binding site, wherein the binding site is located between, within, or surrounding an adenovirus packaging sequence, B) obtaining an adenovirus comprising: a) 5' and 3' Ad ITRs, b) a different adenovirus packaging element other than the packaging element in the adenovirus vector of A), c) a promoter operatively linked to a heterologous gene; C) propagating the vector

from step A) and the vector from step B) in a cell-line, which expresses a repressor for inhibiting the packaging of the vector from A); thereby obtaining replicant defective adenovirus vector; 2) The method of 1, wherein the cell-line in step C) either endogenously or exogenously expresses said repressor; 3) A method for reducing tumor size in a mammal comprising: A) isolating the replication defective adenovirus vector comprising a heterologous gene from 1), wherein the heterologous gene is an anti-tumor gene, B) preparing the vector of A) in a pharmaceutically acceptable carrier; and C) directly administering to a tumor in a mammal the vector from step B); 4) A method for expressing Factor VIII in a mammal comprising: A) isolating the replication defective adenovirus vector comprising a heterologous gene from 1), wherein the heterologous gene is Factor VIII, B) preparing the vector of A) in a pharmaceutically acceptable carrier; and C) intravenously (i.v.) administering to a mammal the vector from step B), wherein expression of said heterologous gene results in increase expression of Factor VIII in the mammal; 4) A replication defective adenoviral vector comprising an adenovirus packaging sequence containing a plurality of COUP-TF binding sites comprising an A repeat VI element; and does not reasonably provide enablement for the full scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention relates to a method of regulating replication defective adenovirus production and methods of DNA delivery using the adenovirus vectors.

With respect to the claims encompassing a method of regulating adenovirus packaging of a replicant defective adenovirus vector comprising the steps of: a) obtaining an adenovirus vector containing an adenovirus packaging element comprising a repressor binding site, B) obtaining an adenoviral vector comprising: a) 5' and 3' Ad ITRs, b) a different adenovirus packaging element, c) a promoter operatively linked to a heterologous gene; C) propagating the helper vector and the adenoviral vector in a cell line; D) repressing the packaging of the helper adenovirus vector from by a repressor which binds to the repressor binding site contained in the helper adenovirus vector, the full breadth of the claims are not enabled and are missing steps that are considered essential for one skilled in the art to practice the claimed methods. The as-filed specification contemplates specifically repressing the production of a helper virus while allowing the production of an adenovirus vector during the preparation of the virus (page 4) and to reduce RCA in preparation of Ad virus by constructing such vectors and a helper virus with no overlap in the packaging sequences to eliminate homologous recombination (page 5). In addition, the disclosure contemplates carrying the method in one cell line or the propagating step may be carried out in a first cell line and the repressing step may be carried out in a second cell line (page 6). Furthermore, the as-filed specification contemplates that a virus (e.g. gutted gene therapy virus) may contain a hexamer of A repeat I in direct orientation, while a helper virus (virus #2) may contain a dimer of A repeats V, VI, VII or a multimer of AVI in an inverted orientation. Thus both viruses carry functional packaging domains, but overlap homologues recombination is greatly minimized since different packaging sequences and DNA orientation are used (pages 16-17).

With respect to the claims encompassing the method set forth above, the as-filed specification provides sufficient guidance for regulating packaging of a replication defective adenovirus packaging and not for the full breadth of the claims because the as-filed specification only contemplates producing replication defective adenoviruses and lacks sufficient guidance for one skilled in the art to make replication competent adenoviruses. In addition, the main goal of the claimed invention is to avoid producing replication competent adenoviruses (e.g. page 13).

Furthermore, with respect to the claimed methods reading on propagating the helper adenovirus vector and the DNA delivery vector in a cell-line; and repressing the packaging of the helper virus by using a repressor which binds to the repressor binding site contained in the helper virus; the as-filed specification provides sufficient guidance for one skilled in the art to propagate the helper adenovirus and DNA delivery adenovirus vector in a cell line in the presence of a repressor for the helper adenovirus vector. However, the as-filed specification fails to provide sufficient guidance for one skilled in the art to propagate both adenoviral vectors in a cell line without a repressor because both vectors would be packaged resulting in replication competent adenoviral vectors. Both vectors would be packaged because a repressor for the helper virus is not present to inhibit the packaging of the helper virus. Thus, producing replication competent adenoviral vectors, which is what the claimed invention is not directed toward and in fact is trying to prevent. Therefore, the claimed methods are only enabled for propagating the helper adenovirus and the DNA delivery adenovirus vector in a cell-line either exogenously or endogenously expressing a repressor (e.g. COUP-TF or lac repressor) for said helper virus and not the full scope of the claimed methods.

Even if the applicants are able to overcome the concerns for preventing packaging of the helper adenovirus when propagating both vectors in the same cell line, there is another problem with the claimed methods (e.g. claim 4 and 5). These claims read on propagating both vectors in a cell line, then repressing the packaging of the helper adenovirus vector in a second cell line. However, the claims are missing steps for how the recombinant viruses from the propagating step are removed from the first cell line and placed into the second cell-line. Therefore, it would take one skilled in the art an undue amount of experimentation to practice the claimed methods because they are lacking steps considered essential for practicing the claimed methods.

Furthermore, and with respect to claims (claims 9 and 19) directed to any adenoviral vector useful for gene therapy and directed to any treatment of a mammal; the state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

With respect to delivering an adenovirus comprising a heterologous gene, the claimed invention reads on a therapeutic method of gene therapy. The as-filed specification is only directed to therapeutic methods of gene therapy using the claimed vector and does not contemplate or provide sufficient guidance for one skilled in the art to practice delivering non-therapeutic heterologous genes to a mammal. More specifically, the as-filed specification states, "...a DNA contain a gene encoding a protein whose expression in the patient may provide a therapeutic benefit. Such proteins may, for example, stimulate an immune response, such as a

vaccine. Gene therapy is one such DNA delivery system. Alternatively, the DNA of interest may not encode a protein yet may provide a benefit to the patient" (page 14). "Many genes and/or DNA segments may be carried by adenoviral vectors. Examples of such genes include; interleukin-2, p53, alpha1-antitrypsin, cystic fibrosis transmembrane conduction regulator (CFTR), and clotting factor VIII" (page 18). Therefore in view of the problems with gene therapy described above, the lack of guidance by the as-filed specification for what therapeutic methods are considered enabled for one skilled in the art to use the claimed vector; and the breadth of the heterologous genes encompassed by the claimed invention, it would take one skilled in the art an undue amount of experimentation to use the claimed adenoviral vector in a representative number of therapeutic methods.

Furthermore, in view of the breadth of the term "heterologous gene", only the gene therapy methods with the genes listed in the as-filed specification will be addressed herein:

First with respect to the claims encompassing a replication competent and/or replication defective adenoviral vector. The as-filed specification only provides sufficient guidance for one skilled in the art to use a replication defective adenoviral vector because as stated in the disclosure replication competent adenoviral vectors are toxic to the patient undergoing gene therapy (pages 3-4, 13, and, 16). In addition, the as-filed specification is only directed to the production of replication defective adenoviral vectors (see pages 3-4). Furthermore, the claims read on using any type of adenoviral vector in any gene therapy method and the art of record displays major hurdles when using adenoviral vectors in any method of gene therapy. The as-filed specification fails to overcome these hurdles and does not provide working examples for

different types of gene therapy methods for one skilled in the art to practice the genus of gene therapy methods contemplated by the as-filed specification.

Furthermore, with respect to interleukin-2 or p53 gene therapy (cancer gene therapy). The state of art teaches at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. Nonetheless, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).
> Vile further discusses:
> A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

In view of the concerns set forth by the art of record and the as-filed specification does not reasonably address the concerns put forth by the problems associated with cancer gene therapy (e.g. systemic administration of a vector to treat a tumor), the claimed adenoviral vector is not enabled for any route of administration other than intra-tumoral administration of the claimed adenoviral vector.

In addition, with respect to αl-antitrypsin gene therapy at the time the application was filed and currently, the state of the art (Albelda et al., Ann. Intern. Med., Vol. 132: 649-660, 2000) teaches:

> Efficient gene transfer is a basic requirement for effective gene therapy (page 649). The most widely used vector in lung gene therapy has been replication-incompetent recombinant adenovirus. The two primary disadvantages are that they result in only transient gene expression and that when virions are used for direct in vivo application, they elicit a prominent local and system inflammatory response (pages 649-650). Gene transfer in clinical trials for CFTR was inefficient and significant inflammation was noted. Furthermore the investigators could not detect correction of sodium or chloride transport (page 650). Furthermore, α-antityrpsin gene expression studies have displayed only transiently increased and were below what would be required for physiologic correction and no clinical trials of gene therapy for this deficiency have been published (page 651)

Further support of the unpredictability of lung gene therapy, with respect to CFTR gene therapy at the time of filing and currently, the state of the art (Bigger et al., BioDrugs, Vol. 15, 2001, pp. 615-634) teaches:

> Unfortunately, first generation adenoviral vectors display low levels gene expression from the remaining viral genes is still maintained in these viruses, which leads to an immune response. Additional deletions of the E2, E3 or E4 results in diminished inflammatory response but many E4 deleted vectors also demonstrate more rapid loss of gene expression even though viral DNA appears to be maintained in the cell. This vector leads to transient gene expression of CFTR lasting usually up to 15 days maximum with repeat application leading to humoral immune response and severely depressed transduction efficiency. The poor transfection of CFTR to the human lungs with adenovirus is probably explained by the lack of cellular receptors for adenovirus binding and internalization on the apical surface of airway epithelial cells. (Tables I, II, and pages

> 620 and 622-623). One of the major problems of gene delivery to the lung plaguing both non-viral and viral vectors is the barrier of the thick mucus in the airway of CF patients creating a serious impediment to physical contact with the cells (page 628).

Since the claimed invention is directed to and provides working examples for diminishing the production of RCA when producing replicant defective adenoviral vectors, the as-filed specification does not provide sufficient guidance for how one skilled in the art would be able to overcome the major hurdles for lung gene therapy (e.g. CFTR or alpha-antityrpsin). More specifically, the claims read on any type of adenoviral vector and in view of the art of record, there are major problems with transient gene expression, pre-existing antibodies to the adenoviral vector, overcoming the thick mucus barrier of CF patients. Furthermore, the as-filed specification fails to provide any working examples for treating any mammal with a genetic deficiency in the lungs with the claimed vector and the art of record is absent about using gene therapy for treating alpha-antityrpsin deficiency in a mammal. Therefore, in view of the In re Wands Factors, the specification fails to provide sufficient guidance for one skilled in the art to use the claimed adenoviral vector in any lung gene therapy method (e.g. CFTR or anti-trypsin).

In addition, with respect to Factor VIII gene therapy using a replication defective adenoviral vector, the state of the art display problems with achieving high and sustained levels of factor delivery and issues related to efficacy (Hortelano et al. Art. Cells. Blood Subs, Immob. Biotech, Vol. 28: 1-24, abstract, 2000). Hortelano teaches:

> There is no requirement to deliver FVIII intracellularly into any particular tissue of the recipient (page 3). Adenovirus is very immunogenic, eliciting both humoral and cellular immune response, rendering subsequent treatments largely ineffective due to neutralizing antibodies developed against the viral vector. Therefore, despite being a highly efficient gene transfer vector, the adenoviral vector can only achieve transient transgene delivery. However, encouraging results were obtained in hemophilic dogs, achieving supraphysiological levels of FVIII using intravenous injection (page 9).

In view of the state of the art at the time the application was filed for Factor VIII gene therapy using am adenoviral vector the as-filed specification fails to provide sufficient guidance for using any route of administration other than intravenous administration of the claimed adenoviral vector further comprising a nucleotide sequence encoding a Factor VIII protein.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed recombinant adenovirus vector generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the for scope listed above. Given that gene therapy wherein any carrier (adenoviral vector) is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any adenoviral vector cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

The applicants' traversal (paper nos. 10 and 12) is not found persuasive to the rejection under 112 first paragraph enablement rejection for the reasons set forth above and because it is not applicable to the rejection set forth above.

The rejection under 112 second paragraph for claims 8-18 is moot because of the amendment to the claims.

However, in view of the amended claims (claims) and newly filed (claims 21-37) a new ground of rejections follow:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 21, and claims dependent therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as their invention.

Claims 1, 21, and claims dependent therefrom are indefinite because the claims do not particularly point out the order of steps listed in each claim. The claims comprises of steps a-d, however, the order for which these steps are carried out is not defined by the claims. Suggest amendment the claims as followed: 1) A method of regulating adenovirus packaging of a replicant defective adenovirus vector comprising the steps of: A) obtaining an adenovirus vector containing an adenovirus packaging element comprising a repressor binding site, wherein the binding site is located between, within, or surrounding an adenovirus packaging sequence, B) obtaining an adenovirus comprising: a) 5' and 3' Ad ITRs, b) a different adenovirus packaging element other than the packaging element in the adenovirus vector of A), c) a promoter operatively linked to a heterologous gene; C) propagating the vector from step A) and the vector from step B) in a cell-line, which expresses a repressor for inhibiting the packaging of the helper virus.

Claims 1, 21 and claims dependent therefrom are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps is how step d) is performed. Step d) is repressing packaging of the helper adenovirus vector be a repressor, however, the claim does not define how the repressing step occurs.

Claims 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the viruses from step c) are removed from the first cell-line and placed in the second cell-line.

The applicants' traversal (paper nos. 10 and 12) is not found persuasive to the rejection under 112 second paragraph for the reasons set forth above and because it is not applicable to the rejection set forth above.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's

supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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9/30/02

DAVE T. NGUYEN
PRIMARY EXAMINER